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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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# Limited effect of patient and disease characteristics on compliance with hospital antimicrobial guidelines

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**Abstract** *Objective:* Physicians frequently deviate from guidelines that promote prudent use of antimicrobials. We explored to what extent patient and disease characteristics were associated with compliance with guideline recommendations for three common infections. *Methods:* In a 1-year prospective observational study, 1,125 antimicrobial prescriptions were analysed for compliance with university hospital guidelines. *Results:* Compliance varied significantly between and within the groups of infections studied. Compliance was much higher for lower respiratory tract infections (LRTIs; 79%) than for sepsis (53%) and urinary tract infections (UTIs; 40%). Only predisposing illnesses and active malignancies were associated with more compliant prescribing, whereas alcohol/ intravenous drug abuse and serum creatinine levels >130 μmol/l were associated with less compliant prescribing. Availability of culture results had no impact on compliance with guidelines for sepsis but was associated with more compliance in UTIs and less in LRTIs. Narrowing initial broad-spectrum antimicrobial therapy to cultured pathogens was seldom practised. Most noncompliant prescribing concerned a too broad spectrum of activity when compared with guideline-recommended therapy. *Conclusion:* Patient characteristics had only a limited impact on compliant prescribing for a variety of reasons. Physicians seemed to practise defensive prescribing behaviour, favouring treatment success in current patients over loss of effectiveness due to resistance in future patients.

**Keywords** Guidelines · Antibiotic policy · Compliance · Drug therapy · Medical decision-making

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## Introduction

Targeting inappropriate antimicrobial use is an important feature of current infection control in hospital care [1]. Antimicrobial treatment guidelines have been developed that strongly promote prudent antimicrobial prescribing [2–5]. At the hospital level, guidelines are developed incorporating the results of local bacterial resistance patterns. After in vitro culture and test results are available (herein referred to as culture-driven therapy), guidelines recommend that therapy should then be guided by the pathogen's susceptibility pattern to antimicrobials [6, 7]. They promote prescribing the narrowest-spectrum drug that adequately covers the isolated pathogen and that reaches the target site. In culture-driven therapy, patient characteristics are of little importance because antimicrobials should simply be chosen by their ability to eradicate the isolated pathogen.

Unfortunately, physicians often do not comply with guideline recommendations [8], nor does availability of culture results automatically lead to adjustment of antimicrobial therapy towards the preferred drug [9, 10]. Many interventions to improve the use of guidelines have been employed, some successfully [11, 12], but there is still room for improvement [13, 14]. It has been suggested that noncompliance may be driven by the guidelines' inability to cover all encountered clinical conditions [15]. This implies that guideline compliance may be limited to a certain ceiling that depends on

the applicability of the guidelines to the infectious disease case-mix.

To date, little attention has been given to the impact of patient and disease characteristics on compliance, although there are indications that compliance with guidelines varies for different infectious diseases, such as skin and soft tissue infection, sepsis, and urinary tract infection (UTIs) [8]. Also, in primary health care, guidelines are more successful in some therapeutic areas than in others [16]. Information on the relevance of patient and disease characteristics helps to increase our understanding of noncompliance with guideline recommendations and to target interventions to improve prescribing. Additionally, the main study findings have been used successfully as feedback material to strengthen guideline use in our university hospital [17].

In this study we explored to what extent patient and disease characteristics were associated with compliance with guideline recommendations for three commonly encountered infections. Second, we evaluated the effectiveness and safety of prescriptions that were not in line with the guidelines' recommendations.

## Methods

### Study design

We performed a prospective observational study of physicians' antimicrobial prescribing behaviour. Patient and disease characteristics were collected for all prescriptions of an antimicrobial agent. We then compared prescribed therapy with guideline recommendations. In cases of culture-driven therapy, a division was made between initial antimicrobial prescriptions to therapy-naïve patients and follow-up prescriptions, that is, those preceded by earlier empiric or culture-driven antimicrobial therapy for that particular infection episode.

### Study setting and sample

*Population* The study covered a 1-year period (February 2001–February 2002) and was conducted in the departments of general internal medicine, including haematology, gastroenterology, nephrology, and pulmonology, and in the intensive care unit of the University Medical Centre Groningen, the Netherlands (Table 1). Patients were included in the study when they were prescribed an antimicrobial agent to treat one of the three most prevalent infectious diseases: sepsis, UTI, or lower respiratory tract infection (LRTI). Antimicrobials prescribed for these infections included systemic antibiotics and antimycotics (ATC J01, J02, J04) [18].

*Setting* In the hospital, a hard-copy antimicrobial guideline published in 1999 was available but had not been actively implemented. Routine clinical microbiology support was available upon request; systematic feedback of culture results was offered only for patients with positive bloodstream infections. There was no routine involvement of pharmacy staff in antimicrobial prescribing, and there were no ongoing activities that addressed antimicrobial policies. Therapeutic drug monitoring facilities were offered only on request.

**Table 1** Description of case characteristics (*UTI* urinary tract infection, *LRTI* lower respiratory tract infection)

| | Sepsis | UTI | LRTI |
|---|---|---|---|
| Prescriptions | *N*=308 | *N*=191 | *N*=626 |
| Male | 179 (58%) | 87 (45%) | 375 (60%) |
| Mean age in years | 59 (SD 18) | 60 (SD 18) | 64 (SD 17) |
| Infection the reason for admission | 164 (53%) | 76 (40%) | 494 (79%) |
| Length of stay in days[a] | 22 (11–40) | 23 (12–41) | 18 (10–34) |
| Deaths | 62 (20%) | 15 (8%) | 89 (14%) |
| Patients | 120 | 133 | 314 |

[a]Median and interquartile range

*Guideline* The local hospital guidelines give general recommendations for good clinical practice of infectious diseases (Appendix) [19]. They recommend taking timely culture samples, checking results, and adapting (stopping, changing, or continuing) antimicrobial therapy when appropriate. In separate chapters, they cover evidence-based specific antimicrobial therapy for a wide range of infections based on national and international guidelines and adapted when necessary to local antimicrobial resistance patterns. The guidelines are composed by a working group of professionals from different relevant specialties in the hospital.

### Data collection

Patient, disease, and prescribing data were extracted from paper medical charts. Bacterial culture and sensitivity test results and clinical laboratory values were extracted from the hospital's electronic information system.

### Outcome measures

Prescriptions were compared with guideline recommendations for specific indications or cultured pathogens by an independent pharmacist observer. All prescriptions were assessed individually, and previous, concurrent, or combined antimicrobial therapy was taken into account as well as the availability of in vitro bacterial test and culture results. In a pilot study, the reliability of this assessment method was proven to be good (overall kappa 0.72) [20]. In cases of culture-driven therapy, in vitro bacterial culture and sensitivity test results overruled guideline recommendations when isolated pathogens were insensitive to guideline-recommended agents. Noncompliant prescribed antimicrobials were compared with guideline-recommended drugs on three criteria relevant for antimicrobial

therapy: safety, efficacy, and spectrum of covered pathogens. To this purpose, the expert classified prescribed antimicrobials as having a safety profile better than, similar to, or poorer than the guideline-recommended agents. Similarly, for the efficacy criterion, agents were considered less effective when they did not covering the expected or cultured pathogens or when they were less able to penetrate the infection site. The bacterial spectrum was considered too narrow when cultured or expected pathogens were inadequately covered. Therapy was considered too broad when, for a specific indication, more nonpathogenic bacteria were affected than were affected by guideline-recommended agents.

### *Patient and disease characteristics*

The following determinants were included:

1. Patient characteristics included age and comorbid diseases known to have an impact on the clinical outcome of the infections studied, such as active malignancy, cerebrovascular accident, and congestive heart failure [7]. Immunosuppressive therapy, urinary catheter in situ, and predisposing illnesses (defined as surgery, trauma, or solid organ transplant prior to initiation of antimicrobial therapy) were considered relevant comorbidities as well [21].
2. Disease severity was measured by a number of proxies, including fever (>38.5°C) and significantly elevated levels of inflammation parameters (C-reactive protein >100 mg/l and leukocyte count <4 or >12*$10^9$/l). Proxies for a more severely ill patient were an increased length of stay (longer than the 11-day average at the department of internal medicine) and patient death during hospital stay. Proxies for renal or liver disorder were serum creatinine levels >130 μmol/l and elevated liver enzymes (transaminases AST >60 U/l and ALT >80 U/l). Disease severity proxies were considered to be clinically relevant if levels were outside the stipulated range in the 3 days prior to initiating the antimicrobial prescription and, for fever, for 24 h prior to prescribing. Validated disease severity score indices, such as the pneumonia severity index (PSI) or APACHE [21, 22], were not routinely used in all wards and were therefore not used.

### *Analyses*

The analysis was performed at the prescription level, implying that more than one prescription per patient could be included. For sepsis, UTI, and LRTI, levels of compliance with specific guideline recommendations were analysed, considering empiric versus culture-driven therapy, aetiology, and isolated pathogens. Descriptive statistics (absolute number of prescriptions and percentages), chi-squares (*p*-values), and odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. The effect of patient and disease characteristics were assessed with a multivariate logistic regression model, including those characteristics that had a *p*-value <0.25 in the univariate analysis.

## Results

### Characteristics

Eleven hundred and twenty-five antimicrobials were prescribed to 120 patients with sepsis, 133 patients with UTI, and 314 patients with LRTI (Table 1). The mean patient age was 60 years. In case of sepsis and UTI, roughly half of the antibiotics were prescribed to patients for nosocomial infections. In cases of LRTI, the majority (79%) of prescriptions were for community-acquired infections. Duration of hospital stay was relatively long, which is understandable in view of the patients included, such as solid organ transplant and haematology patients. The majority of UTI patients were female, whereas more male patients were treated for sepsis and LRTI.

### Compliance with guideline recommendations

In 164/308 (53%) prescriptions for sepsis, 76/191 (40%) for UTI, and 494/626 (79%) for LRTI ($p<0.001$), a guideline-recommended antimicrobial agent was used. When each group of infections was looked at separately in more detail, guidelines were followed to a different extent for various clinical problems (Table 2). Treatment complied poorly with guideline recommendations for proven *Enterobacteriaceae* infections in patients with sepsis. The guidelines recommended tobramycin as first-line treatment, but that recommendation was followed in only 20% of the prescriptions. Empiric therapy was generally poorly compliant for lower UTI, in which the recommended, mainly narrow-spectrum antibiotics were not used. The broad-spectrum ciprofloxacin was used in almost half of the prescriptions for UTI (data not shown), though it was only recommended in UTI as second-line treatment for pyelonephritis and prostatitis. Co-amoxiclav was preferred for treating feverish patients with UTI and a catheter in situ, instead of the guideline-recommended combination of amoxicillin and tobramycin.

For LRTI, compliance with guideline recommendations was by far the best. Notably, for empiric therapy of hospital-acquired pneumonia (HAP), community-acquired pneumonia (CAP), or acute bronchitis, the guideline recommended the same broad-spectrum agent, co-amoxiclav, which was prescribed in 45% of all LRTI cases. However, in culture-driven therapy of LRTI, differences in prescribing compliance were observed ($p=0.002$). When treating streptococci (50%) and *Staphylococcus aureus* (43%) infections, physicians followed guideline recommendations less than when other pathogens were cultured (58–87%).

**Table 2** Compliance with guideline recommendations for infections, considering aetiology or isolated pathogen (*UTI* urinary tract infection, *LRTI* lower respiratory tract infection, *CAP* community-acquired pneumonia, *HAP* hospital-acquired pneumonia, *CNS* coagulase-negative staphylococci)

| Sepsis | | | UTI | | | LRTI | | |
|---|---|---|---|---|---|---|---|---|
| Empiric therapy | | | | | | | | |
| Unknown origin | 20 | (65%) | Lower UTI | | | CAP | 215 | (82%) |
| Lungs | 38 | (45%) | -Uncomplicated | 13 | (39%) | HAP | 78 | (83%) |
| Urinary tract | 69 | (41%) | -Complicated | 52 | (12%) | Acute bronchitis | 80 | (85%) |
| Skin, bone, joints | 9 | (89%) | (Male/catheter) | | | Cystic fibrosis | 47 | (94%) |
| Abdomen | 30 | (70%) | Pyelonephritis/epididymitis | 7 | (71%) | Tuberculosis | 2 | (100%) |
| | $p$=0.006[a] | | | $p$<0.001 | | | $p$=0.38 | |
| Culture-driven therapy | | | | | | | | |
| Enterobacteriaceae | 35 | (20%) | Enterobacteriaceae | 65 | (40%) | Mixed infections | 51 | (80%) |
| Mixed infection | 25 | (56%) | (Especially *E. coli*) | | | *Pseudomonas* | 31 | (87%) |
| *S. aureus* | 21 | (86%) | Mixed infections | 21 | (52%) | *S. aureus* | 28 | (43%) |
| Streptococci | 16 | (50%) | Enterococci | 15 | (73%) | Streptococci | 24 | (50%) |
| CNS | 15 | (60%) | Other | 18 | (67%) | *Enterobacteriaceae* | 20 | (65%) |
| Fungal infections[b] | 10 | (100%) | | | | Fungal infections[b] | 17 | (71%) |
| Other | 20 | (55%) | | | | Other | 33 | (64%) |
| | $p$<0.001 | | | $p$=0.05 | | | $p$=0.002 | |

[a] $p$-values are based on chi-square calculations of levels of compliance with guidelines within specific infection groups, considering whether therapy was empiric or culture-driven
[b] Candida, Aspergillus, etc

## Compliance with guideline recommendations between departments

Compliance with guideline recommendations did not differ between departments (Fig. 1). UTI compliance was compared only between the departments of general internal medicine and nephrology because too few prescriptions for comparison were prescribed in the other departments.

## Compliance with guideline recommendations and availability of in vitro culture test results

Availability of culture results had no impact on compliance in case of sepsis, but was associated with more compliance in UTI and less compliance in LRTI (Table 3). No significant differences in compliance in culture-driven therapy were observed for prescriptions to patients who were pretreated (follow-up) with an antimicrobial agent or to those who were therapy-naïve (initial).

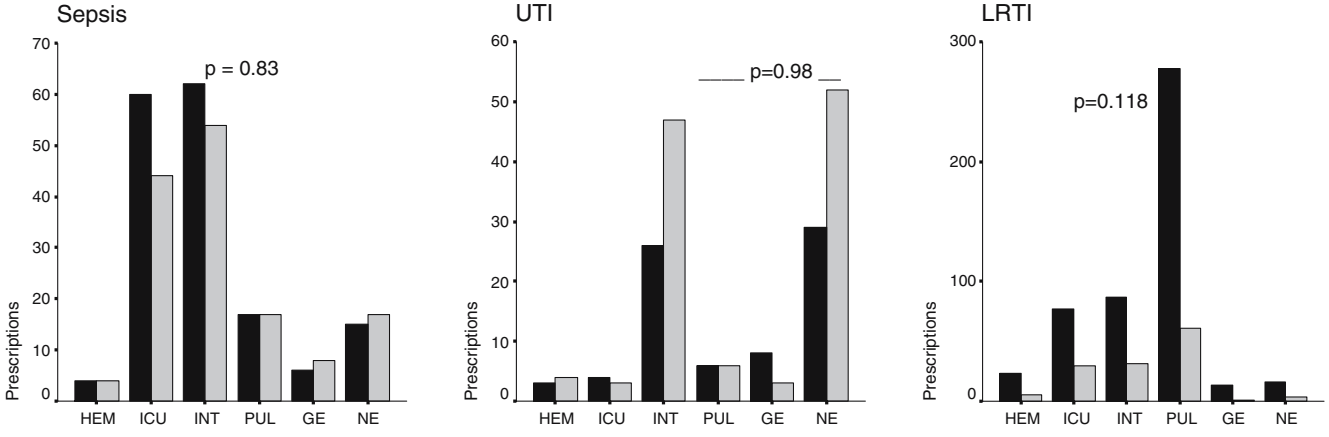


**Fig. 1** Compliant prescriptions (*black bars*) and noncompliant prescriptions (*grey bars*) across different departments. *P*-values for differences in level of compliance between departments are based on chi-square tests. Guideline compliance is similar for the three infections across the different subdepartments. For urinary tract infections (*UTI*), only general internal medicine (*INT*) and nephrology (*NE*) departments are compared because the other departments had too few prescriptions to allow for a reliable comparison. (*HEM* haematology, *GE* gastroenterology, *ICU* intensive care unit, *PUL* pulmonology)

**Table 3** Comparison of antimicrobial prescriptions with guideline recommendations and impact of culture results (*UTI* urinary tract infection, *LRTI* lower respiratory tract infection)

| | Empiric therapy *N* (% compliant) | Culture-driven therapy *N* (% compliant)[a] | | | Odds ratio$_{doc/emp}$ (95% CI)[b] |
|---|---|---|---|---|---|
| | | Overall | Initial | Follow-up | |
| Sepsis | 166 (52%) | 142 (54%) | 32 (53%) | 110 (55%) | 1.07 (0.69–1.69) $p$=0.89[c] |
| UTI | 72 (22%) | 119 (50%) | 69 (45%) | 50 (58%) | 3.56 (1.84–6.90) $p$=0.16[c] |
| LRTI | 422 (84%) | 204 (68%) | 60 (73%) | 144 (65%) | 0.39 (0.26–0.58) $p$=0.26[c] |

[a]Culture-driven therapy is divided into prescriptions that were not preceded by an antimicrobial prescription (initial) and those that were preceded by another antimicrobial prescription (follow-up). (See Methods section)
[b]The odds ratios and 95% confidence intervals are given of the impact of the availability of culture results on prescribing compliance compared with prescribing compliance for empiric therapy
[c]Pearson chi-square

## Patient and disease characteristics and compliance

Empiric antimicrobial therapy was more often in line with guideline recommendations for septic patients with predisposing illnesses (trauma, surgery, solid organ transplant) and LRTI patients with active malignancy. In cases of alcohol/intravenous drug abuse, empiric therapy for sepsis and culture-driven therapy for LRTI were less compliant (Table 4). Increased serum creatinine levels (>130 μmol/l) were associated with less compliant culture-driven pre-

**Table 4** The effect of age, comorbidity, and disease severity on antimicrobial drug choice (*UTI* urinary tract infection, *LRTI* lower respiratory tract infection, *CVA* cerebrovascular accident)

| | Determinants | *N* (% compliant) | Multivariate odds ratio (95% CI), *p*-value |
|---|---|---|---|
| Sepsis | | | |
| Empiric (*n*=166) | Predisposing illness | 37 (70%) | 2.99 (1.27–7.05), 0.01 |
| | Alcohol/ intravenous drug abuse | 6 (17%) | 0.07 (0.01–0.79), 0.03 |
| | Immunosuppressive medication | 46 (44%) | 0.49 (0.23–1.03), 0.06 |
| | ALT >60 U/l | 45 (62%) | 2.03 (0.95–4.32), 0.07 |
| | Length of stay >11 days | 109 (57%) | 1.78 (0.88–3.58), 0.11 |
| Culture-driven (*n*=142) | Active malignancy | 6 (100%) | 3,226 (0–9*10$^{22}$), 0.73 |
| | ALT >60 U/l | 39 (69%) | 2.37 (0.78–7.26), 0.13 |
| | Creatinine >130 μmol/l | 74 (45%) | 0.40 (0.20–0.83), 0.01 |
| | Age >65 years | 52 (46%) | 0.69 (0.33–1.45), 0.32 |
| | AST >80 U/l | 28 (64%) | 1.09 (0.33–3.68), 0.88 |
| UTI | | | |
| Empiric (*n*=72) | Age >65 years | 43 (16%) | 0.71 (0.20–2.50), 0.59 |
| | Active malignancy | 8 (0%) | 0 (0–6*10$^{24}$), 0.80 |
| | Temperature >38.5°C | 30 (13%) | 0.29 (0.07–1.18), 0.08 |
| | Leukocytes <4 or >12*10$^9$/l | 25 (32%) | 2.95 (0.79–11), 0.11 |
| Culture-driven (*n*=119) | Predisposing illness | 49 (43%) | 0.61 (0.27–1.37), 0.23 |
| | Temperature >38.5°C | 18 (67%) | 1.71 (0.55–5.27), 0.35 |
| | Leukocytes 4< or >12*10$^9$/l | 22 (64%) | 1.90 (0.66–5.46), 0.24 |
| | AST >80 U/l | 5 (100%) | 1,189 (0–4*10$^{16}$), 0.66 |
| LRTI | | | |
| Empiric (*n*=422) | Age >65 years | 217 (87%) | 1.56 (0.89–2.73), 0.12 |
| | Active malignancy | 49 (96%) | 4.40 (1.03–18.83), 0.045 |
| | CVA | 39 (77%) | 0.50 (0.21–1.16), 0.11 |
| | Diabetes | 80 (89%) | 1.67 (0.78–3.58), 0.19 |
| | Predisposing illness | 35 (91%) | 1.65 (0.48–5.70), 0.43 |
| Culture-driven (*n*=204) | Alcohol/intravenous drug abuse | 15 (40%) | 0.32 (0.10–0.96), 0.04 |
| | Chronic hepatic insufficiency | 3 (33%) | 0.73 (0.06–9.66), 0.81 |
| | Urinary catheter | 36 (78%) | 1.73 (0.72–4.15), 0.22 |
| | Creatinine >130 μmol/l | 35 (49%) | 0.37 (0.17–0.81), 0.01 |

Patient/disease characteristics included in the univariate analysis: age, active malignancy, CVA, congestive heart failure, immunosuppressive therapy, urinary catheter in situ, predisposing illnesses (defined as surgery, trauma, or solid organ transplant prior to initiation of antimicrobial therapy). Disease-severity characteristics included in the univariate analysis: fever (>38.5°C), C-reactive protein >100 mg/l, leukocyte-count <4 or >12*10$^9$/l, length of stay >11 days, death during hospital stay, serum creatinine levels >130 μmol/l, AST >60 U/l, ALT >80 U/l. Disease severity proxies were considered to be clinically relevant if levels were outside the stipulated range up to 3 days prior to initiating the antimicrobial prescription and, for fever, for 24 h prior to prescribing

scribing in patients with sepsis and LRTI. Age, comorbid disease, and disease severity had no impact on empiric or culture-driven therapy of UTI.

How rational is noncompliant therapy?

In the majority of noncompliant prescriptions, therapy had a similar safety profile and comparable efficacy as guideline-recommended therapy, but excessively broad-spectrum agents were used for the expected or isolated pathogens. Approximately a third of all prescriptions (sepsis 41%, UTI 40%, LRTI 27%) were too broad for empiric therapy and roughly two-thirds for culture-driven therapy (sepsis 65%, UTI 71%, LRTI 59%) (Table 5). In 11–14% the prescribed antimicrobials assessed as noncompliant were in fact comparable to guideline-recommended agents on all three criteria. In 10 (13%) prescriptions for sepsis and in 22 (one-third) prescriptions for LRTI, the noncompliant empiric therapy had too narrow a spectrum, but it had a safety profile similar to guideline-recommended therapy. In cases of sepsis, co-amoxiclav was prescribed eight times, mainly for catheter-related urosepsis, instead of the guideline-recommended amoxicillin with either tobramycin or ciprofloxacin. In cases of LRTI, national and professional group guidelines for CAP were followed (for instance, amoxicillin was prescribed instead of the recommended co-amoxiclav for CAP), but those recommendations were not appropriate according to the local guidelines for CAP.

## Discussion

The hypothesis that patient and disease characteristics were relevant for prescribing in line with recommendations could be confirmed only for a limited number of characteristics; predisposing illnesses and active malignancies were associated with more compliant prescribing, whereas alcohol/intravenous drug abuse and serum creatinine levels >130 μmol/l were associated with less compliant prescribing. In our study, compliance with guideline recommendations differed considerably between and within the groups of infections studied. Compliance was much higher for LRTI than for sepsis and UTI. Noncompliant prescribing was mainly too broad compared with guideline-recommended therapy and seldom too narrow. Availability of culture results led to more targeted drug choices—that is, to use of narrower-spectrum agents—only for UTI.

The fact that few relevant patient and disease characteristics could be identified may in part be due to physicians' lack of awareness of disease severity criteria in the guideline or to incomplete documentation, as found elsewhere [23]. Patients were to a large extent treated with unduly broad-spectrum therapy with limited consideration of local bacterial resistance patterns. Such defensive behaviour is also described as occurring elsewhere [8, 14, 23, 24]. When available culture results recommended the use of more targeted narrow-spectrum therapy the advice was not followed. The recommended "streamlining" approach of narrowing initial broad-spec-

**Table 5** Noncompliant antimicrobial therapy (*UTI* urinary tract infection, *LRTI* lower respiratory tract infection)

| Prescribed antimicrobials compared with guideline-recommended therapy[a] | Sepsis | UTI | LRTI |
|---|---|---|---|
| Empiric therapy | | | |
| Spectrum too broad only | 32 (41%) | 22 (40%) | 18 (27%) |
| Less efficacious because of covering a too-narrow range of pathogens | 10 (13%) | – | 22 (33%) |
| Similar (for efficacy, safety, and bacterial spectrum criteria) | 9 (11%) | 7 (13%) | 10 (13%) |
| Spectrum too broad with a less favourable safety profile | 8 (10%) | 4 (7%) | 3 (5%) |
| Spectrum too broad without adequately covering the expected pathogens for a specific indication but with a more favourable safety profile | 3 (4%) | 6 (11%) | – |
| Spectrum too broad with a more favourable safety profile | 2 (3%) | 6 (11%) | – |
| Other | 14 (18%) | 11 (20%) | 13 (20%) |
| Total | 79 | 56 | 66 |
| Culture-driven therapy | | | |
| Spectrum too broad only | 42 (65%) | 42 (71%) | 39 (59%) |
| Similar (for efficacy, safety, and bacterial spectrum criteria) | 7 (11%) | 8 (14%) | 11 (17%) |
| Other | 16 (24%) | 9 (15%) | 16 (24%) |
| Total | 65 | 59 | 66 |

[a]Rationale of noncompliant antimicrobials is compared with guideline-recommended antimicrobials on three criteria: safety, efficacy, and bacterial spectrum covered. They can be more, less, or equally safe (adverse event profile/intrinsic toxicity) or effective (covering expected or isolated pathogens), and their spectrum can cover more, less, or a similar number of pathogens (whether relevant for the infection or not) than the guideline-recommended agent. In total, 27 categories (3*3*3) are possible, of which those are shown that describe at least 10% of noncompliant prescriptions within one infection

trum therapy to therapy directed at the isolated pathogen's sensitivity was not practised [2, 19, 25, 26]. Resident physicians in our hospital preferred to stay with their initial therapeutic choices because of the adage, "Never change a winning team" [27]. Defensive behaviour may in some cases be driven by fear of high mortality rates and the fact that inadequate initial bacterial coverage has been correlated with increased mortality [28, 29].

Defensive behaviour might also explain less compliance in the few alcohol/ intravenous drug abusers. Broader-spectrum agents with additional anaerobic coverage were prescribed, which may be prompted by physicians' having in the back of their minds the increased risk of aspiration pneumonia in these patients. Similarly, more compliance for patients with predisposing illnesses seemed also driven by defensive behaviour. In these cases, physicians were possibly more cautious and therefore more inclined to check the guidelines carefully when treating patients with acute complications of previous clinical interventions.

In cases of LRTI, defensive behaviour coincided with the guideline-recommended broad-spectrum empiric therapy with co-amoxiclav. However, therapy was not often streamlined after culture results became available. This explains the steep decline in compliance in culture-driven therapy. A typical example was the treatment of a patient with CAP who was initially treated empirically with co-amoxiclav. Here, when test results become available, the guidelines suggest narrowing therapy down to penicillin G or amoxicillin for streptococci and flucloxacillin for *S. aureus* infections [19, 30], as these narrow-spectrum antibiotics still have, in the Dutch setting, good efficacy against these pathogens [25, 31].

Similarly, in cases of alcohol or intravenous drug abuse, culture-driven therapy for LRTI was not targeted to the isolated pathogens. Although some exotic pathogens were isolated, such as *Serratia liquefaciens* and *Hafnia alvei*, mostly *S. pneumoniae* and *S. aureus* with normal antibiotic sensitivity were found. Thus, no compelling reasons can be given why culture-driven therapy should not be targeted to the reported bacterial sensitivity in this group of patients.

Physicians in our hospital who were reluctant to prescribe tobramycin possibly feared its nephrotoxic side effects even though it was recommended in the guideline [27]. In sepsis cases, this led to prescribing agents of too narrow a spectrum—mainly co-amoxiclav—indicating that defensive considerations are not the single driving force in prescribing behaviour. In line with this finding, elevated serum creatinine (>130 μmol/l) levels were associated with less compliance for culture-driven therapy of sepsis and LRTI. Physicians in these cases seemed more inclined to choose nonrecommended antibiotics than to make dose adjustments for recommended antibiotics (for example, for tobramycin). One could argue that this reluctance to use aminoglycosides is reasonable in view of their toxicity and often subsequent need for dose adjustments. The guideline, however, emphasises the effectiveness of aminoglycosides for seriously ill patients because of their rapid bactericidic action and widening of the bacterial spectrum when added to betalactams [32]. Therapeutic drug monitoring is recommended to maintain appropriate and safe drug levels and is generally performed in aminoglycoside therapy in our hospital. In addition, resistance to aminoglycosides is very low in the Netherlands (2–7%) [33].

Empiric therapy of LRTI was also too narrow in a third of the cases. This may be due to misperceptions about the pathogens present in the local population, which differs from the general population because of the overrepresentation of diabetics, patients with chronic obstructive pulmonary disease (COPD), and alcoholics. In an earlier study we found that physicians, when asked to "treat" a paper CAP case, thought *S. pneumoniae* was the most likely causative pathogen [27]. Therefore, they would consider therapy with amoxicillin or even benzylpenicillin appropriate [27], as recommended in national Dutch and professional pulmonology society guidelines for CAP [30, 34]. However, the guideline recommends co-amoxiclav because *Haemophilus influenzae* and *Klebsiella pneumoniae* are frequently isolated in these patients in our hospital. This illustrates the need to stress to physicians that local guidelines sometimes differ from national guidelines [35]. The long duration of stay of patients with LRTI may be explained by the overall case-mix, in which patients with considerable comorbidity, such as COPD or cystic fibrosis or in whom *Pseudomonas* was cultured, were overrepresented.

In cases of UTI, physicians seemed to prefer ciprofloxacin despite the growing evidence of resistance associated with inappropriate and abundant use of fluoroquinolones [25, 36, 37]. Routine decision-making by physicians may play a role here. Such routine-like prescribing behaviour has been reported in primary care [38] and was mentioned by physicians in an earlier study [27]. In the Netherlands, use of co-trimoxazole for treating male patients with lower UTIs, as recommended by the guideline, is quite acceptable [39]. Both co-trimoxazole and ciprofloxacin have good tissue-penetrating properties, which is important in these patients, in whom the prostrate is often affected. Ciprofloxacin is then reserved for those cases in which isolated pathogens are resistant to co-trimoxazole. This choice may be explained by the concern in this guideline to prevent increasing levels of ciprofloxacin resistance.

Low compliance with recommendations for sepsis, UTI, and LRTI may be explained by a perceived lack of quality of the guidelines. As discussed, hospital guideline recommendations were developed in relation to epidemiological data of isolated pathogens and antimicrobial sensitivity patterns in the hospital catchment's population, and they may therefore differ from international and national recommendations. This approach is considered good practice for antimicrobial guidelines [26, 40, 41]. This implies that guideline developers have to invest more effort in communicating to prescribers why local recommendations may differ, particularly in view of specialists' reluctance to use local guidelines when international or professional group guidelines exist [35]. The need for local adaptations may be higher in a university hospital setting, where the patient population is more likely to differ from the general population.

Limitations of this study are that only those aspects of care that were reported in the medical dossier could be considered and that proxies for disease severity were used instead of validated disease severity score systems such as PSI or APACHE or a full clinical picture that included regular visual inspection of a patient's progress. Another limitation is that for UTI, the number of antimicrobials prescribed was limited, which reduced the study's statistical power. This lack of statistical power may have prevented the criterion of an elevated temperature becoming a significant determinant of noncompliant prescribing.

In conclusion, patient characteristics had only a limited impact on compliant prescribing. What seemed to be more important were the preference for some overly broad-spectrum drugs, driven by defensive behaviour and a dislike for other agents (for example, fear of possible toxic drug effects, such as nephrotoxicity from aminoglycosides), and for narrow-spectrum drugs due to additional work involved in streamlining therapy and perceived risk of reduced efficacy. Additionally, awareness of individual and epidemiological culture results and appropriate follow-up need further attention. Efforts to improve compliance with the guidelines should target specific antibiotic drug choices rather than specific patient groups, stressing the full armamentarium available besides guidelines, such as therapeutic drug monitoring, bacterial lab facilities and pro-active support of clinical microbiology and hospital pharmacy staff. The results stress the importance of involving the prescribers in the guidelines development and implementation, providing them with the opportunity to voice their concerns and views on the relation with (inter)national guidelines.

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## Appendix

Hospital guidelines, University Medical Center Groningen [19]

The guideline consists of 17 chapters on antimicrobial therapy and eight chapters on antimicrobial prophylaxis. Additional chapters give recommendations on antimicrobial use for pregnant and breastfeeding women and for renal- and hepatic-impaired patients, and antibacterial sensitivity patterns of isolated pathogens in the hospital. The guideline also gives general recommendations on when and how to take appropriate bacterial culture samples and how to streamline therapy. Literature references are given, on which the guideline recommendations are based. As an example for the three most common type of infections, guideline-recommended agents for empiric therapy are given below. The guideline also gives recommendations on dosing, administration route, and duration of therapy (not shown).

| Type of infection | Recommended drug choice |
|---|---|
| Urinary tract infection (UTI) | |
| Lower UTI | |
| -Uncomplicated | Nitrofurantoin, trimethoprim (or norfloxacin) |
| -Male | Co-trimoxazole |
| -Catheter in situ (with fever) | Amoxicillin + tobramycin |
| Acute pyelonephritis | Cefuroxime + tobramycin, or ciprofloxacin |
| Sepsis | |
| -Urosepsis, no catheter | Cefuroxime or tobramycin |
| -Urosepsis, catheter in situ | Amoxicillin + (ciprofloxacin or tobramycin) |
| -Hospital-acquired pneumonia | Cefuroxime + tobramycin |
| -Abdominal, unknown location | Amoxicillin + tobramycin+ metronidazole |
| -Abdominal, bile duct | Piperacillin + tobramycin |
| Lower respiratory tract infections | |
| Community-acquired pneumonia (suspected *Legionella*) | Co-amoxiclav (+ erythromycin) |
| Hospital-acquired pneumonia, severe or with additional risk factors | Cefuroxime + tobramycin, or ceftazidime |

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